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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,654	02/14/2002	Charles Andrianjara	A0000477-01-CFP	1864

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WARNER-LAMBERT COMPANY
2800 PLYMOUTH RD
ANN ARBOR, MI 48105

EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,654	ANDRIANJARA ET AL.	
	Examiner	Art Unit	
	Deepak R Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31 and 37-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-31 and 42-46* is/are allowed.

6)☒ Claim(s) *37 and 38* is/are rejected.

7)☒ Claim(s) *39-41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *30304 & 30804*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 3, 2004 has been entered.

Claims 1-31 and 37-46 are pending in this application.

The following rejections are withdrawn:

The Declaration under 37 CFR 1.132 filed March 3, 2004, showing that the applicants are the first inventors of all the subject matter that is disclosed in 60/268,821 and is common to 10/075,654, is sufficient to overcome the rejection of claims 1-20, 31 and 37-46 under 35 U.S.C. 102(e) based upon 2002/0078276.

The following rejections are under new grounds:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating arthritis, does not reasonably provide

enablement for a method of treatment of all diseases or complaints involving a therapy by inhibition of MMP-13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. (The reasons provided in the previous office action of May 23, 2003 are incorporated here by reference).

The instant claims are drawn to 'a method for treating a disease or complaint involving a therapy by inhibition of MMP-13' and the specification on page 2, lines 5-9 provides a list of disorders. First, the method recited in the instant claim 37 includes 'diseases or complaints' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The instant claim language covers diseases that are very difficult to treat, e.g., cancer, inflammatory bowel disease, multiple sclerosis, etc. and diseases that are yet to be discovered, for which there is no enablement provided. The list of conditions recited in the claims comprises of generic disease groups such as inflammatory bowel disease, periodontal diseases, and cancer. Further, there is no single common mechanism by which all of the diseases in the instant claims arise. Substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or "not provided", see *Ex parte Jovanovics*, 211 USPQ 907, 909.

The activity for the claimed compounds disclosed in the specification is as MMP inhibitors. Biological assays are provided in the specification in Example 28 and IC_{50} values for MMP-13 inhibition of some of the compounds of the invention are provided in Table 1, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. The disclosure is insufficient

such that one of ordinary skill in the art would not be able to extrapolate the given data to activity of the compounds in all other conditions of the claims. Many of the claimed disorders, e.g., inflammatory bowel disease, multiple sclerosis, cancer, etc. have no common etiology or mechanism and have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the claimed compounds can treat the large list of diseases recited in the claim having diverse mechanisms.

The therapeutic method of the instant claims includes treatment of inflammatory bowel disease, e.g., Crohn's disease, ulcerative colitis, etc. which have been proven very difficult to treat because 'there is no known cause' (see The Merck Manual). Bremner et al. (Expert Opin. Pharmacother. 2002) provide that "New therapies that affect immunomodulation offer the possibility of disease control in those unresponsive to conventional therapy and may reduce the need for further surgery. However, these treatments remain to be fully evaluated" (see page 820). Singh et al. (British Journal of Surgery, 2001) provide that 'the etiology and pathogenesis of inflammatory bowel diseases are incompletely understood' (see page 1558). Robinson (Eur. J. Surg. 1998) indicates that "Despite the growing list of medications and formulations prompted for the treatment of IBD, no single drug or recognized combination has yet been confirmed as dependably clinically effective"; "All physicians who care for UC and CD patients enthusiastically await more optimal regimens for these challenging disorders" (see page 90). This state of the art analysis indicative of the unpredictability related to the treatment of inflammatory bowel diseases.

Further, the list of the diseases includes multiple sclerosis, which has traditionally been very difficult or impossible to treat effectively with chemotherapeutic agents. See e.g., Casanova

et al. (PubMed Abstract enclosed) state that "Multiple Sclerosis (MS) is a disorder in which the pathogenesis is not clearly understood", see the abstract. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method for treating a 'disease' generally, solely based on the inhibitory activity disclosed for the compounds.

Further, the instant claim is also drawn to 'treatment of a cancer' - no compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. In reference to tumor growth and metastasis, Morris et al. (Invasion Metastasis, 1997) stated that "initial arrest and extravasation may be difficult to prevent" (see the PubMed Abstract enclosed). Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Regarding psoriasis, another disease specifically recited in the claims, The Merck Manual provides that "The prognosis depends on the extent and severity of the initial involvement—usually the earlier the age of onset, the greater the severity. Acute attacks usually clear, but permanent remission is rare", which highlights the level of unpredictability in the treatment of the disease.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use in treating a diverse list of conditions.

2) The state of the prior art: There are no known single group of compounds of similar structure which have been demonstrated to treat the wide variety of conditions instantly recited.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Rasmussen et al., in a recent article

(Pharmacol. Ther., Vol. 75, 1997) stated that "Randomized clinical trials, in particular in earlier-stage disease, are required in order to fully characterize the therapeutic potential of this class of agents", see page 74, col. 1. Also, Chambers et al., in their review article (J. National Cancer Inst., Vol. 89, 1997) expressed that "Details of the mechanisms by which MMPs and their inhibitors contribute to creating an environment that favors the initiation and continued growth of primary and metastatic tumors remain to be elucidated, but are of key importance in cancer therapy". Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to protect a potential host from the disorders nor there are doses given for the treatment of the disorders commensurate in scope with the claims.

6) The breadth of the claims: The instant claims embrace the treatment of a multitude of generic conditions.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have

to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Applicant's arguments filed on May 18, 2003 have been fully considered but they were not deemed to be persuasive. Applicant has not provided which are diseases are intended by claim 37. Further, applicant has not provided any competent evidence showing that the MMP-13 inhibitory activity is directly linked to the treatment of the various diseases of the claim 38.

Applicant's arguments based on *In re Brana* have been fully considered but the fact situation in *Brana* case is significantly different as compared to the instant case. Applicants in that case proffered sufficient evidence testing several compounds within the scope of the claims and showed that they exhibited significant antitumor activity. The examiner sees no conflict with Brana, since in that case, the relevant area was indeed cancer, since it was cancer test results that were relied on, not any theory of the underlying biochemical basis. Further, there is no evidence of record that MMP-13 inhibitors are established to work for the treatment of all the diverse diseases of the instant claims.

Allowable Subject Matter

Claims 1-31 and 42-46 are allowed. The references of record do not teach or fairly suggest the instantly claimed compounds.

Claims 39-41 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Information Disclosure Statements filed on March 3 and 8, 2004 have been acknowledged and the copies are enclosed herewith. The cited copending application 10/739,261 has been considered, however, the entry has been crossed off as the application is still pending and all pending applications are preserved in confidence. Accordingly, this will not appear in the reference list of the patent resulting from the instant application. See MPEP §901.03 and 2127, paragraph IV.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

May 31, 2004